withdrawn, it is evident that the Examiner has agreed with Applicants that none of Ibanez (WO 97/18240), Jefferies (U.S. Patent No. 5,981,194), Shen (J. Immun. 152:3017-3023, 1994), Dikic (Nature 383:547-549, 1996), Finkbeiner (Neuron 19: 1031-1047, 1997), and Chalazonitis (Developmental Biol. 204:385-406, 1998), in any proper combination, teach or suggest Applicants' claimed methods that utilize ***Ret-independent intracellular signaling effected by GPI-anchored receptors***.

In the Office Action dated November 27, 2002, however, these references have again been cited against Applicants' claims, based on the further combination with Baloh (PNAS 95:5801-5806, 1998), and it is argued in the Office Action that this combination renders Applicants' claimed invention obvious under 35 U.S.C. § 103. It is apparent, therefore, that the Examiner is of the opinion that Baloh describes pathways for Ret-independent intracellular signaling effected by GPI-anchored receptors. Applicants respectfully submit that Baloh fails to describe such pathways.

As a preliminary matter, Applicants respectfully submit that some basic principles must be followed when making obviousness rejections. Specifically, any cited references must be considered *as a whole*, and must be viewed *without the benefit of hindsight* afforded by Applicants' disclosure. Moreover, the references must *suggest the desirability of making the combination*, and do so with a *reasonable expectation of success*. *Hodosh v. Block Drug Co., Inc.*, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986). When held to this standard, Baloh and the other cited art fail to meet the requisite threshold.

Indeed, Baloh, when taken as a whole, clearly fails to teach the subject matter accorded to it in the Office Action. For example, it is stated in the Office Action that "Baloh et al. teach a method wherein the nervous system cells express GFRα receptors but not Ret receptors," and citation is made to the Abstract, and the last two paragraphs of the

Introduction. It is respectfully submitted that a careful reading of those passages shows that Baloh teaches no such thing, however. The Baloh Abstract states that

> [f]ibroblasts *expressing **Ret** and GFRα3* do not respond to any of the known members of the GDNF family, suggesting that GFRα3 interacts with a unknown ligand or requires a different or additional signaling protein to function

(emphasis added). Thus, contrary to what is asserted in the Office Action, the abstract makes no mention of nervous system cells expressing GFRα receptors but not Ret receptors. Similarly, in the last two paragraphs of its Introduction, Baloh states

> [t]he multicomponent GF receptor system recently characterized accounts for the overlap observed in GDNF and NTN action. The signaling component *is the Ret receptor* tyrosine kinase, and both GDNF and NTN *can activate Ret in transfected cell lines* and cultured superior cervical ganglion neurons (18, 19). Activation *of Ret* by GDNF or NTN requires the presence of a glycosyl-phosphatidylinositol (GPI)-linked ligand binding coreceptor. Two GF receptor α components (GFRαs) have been identified, GFRα1 and GFRα2, and both can mediate GDNF or NTN signaling *through Ret* (20-23), although there is evidence that some specificity exists, with GFRα1 functioning preferentially as a GDNF receptor and GFRα2 as a preferential NTN receptor (7, 22, 23).

See Baloh, page 5801 (emphasis added). Far from teaching cells that express GFRα receptors, but not Ret, this passage explicitly refers to *Ret-dependent* signaling pathways, and thus *teaches away* from the instant invention.

It is also asserted in the Office Action that Baloh teaches, at page 5806, column 1, second paragraph, a method "wherein the nervous system cells are DRG neurons Ret (-/-) and Ret-independent." Again, Applicants respectfully submit that the Examiner is mistaken in this regard. The paragraph in question initially refers to fibroblasts that express both Ret and GFRα3 – clearly not Ret (-/-) DRG neurons. Baloh then goes on to make reference to the work of other authors, stating that the "existence of another Ret-like signaling molecule has

also been proposed to explain the expression of GFRα1 and GFRα2 in several structures without Ret (refs. 22 and 26; J.P.G., R.H.B., P. Kotzbauer, P. Lampe, P. Osborne, J.M., and E.M.J., unpublished work)." This also is not a description of Ret (-/-) DRG neurons, as suggested in the Office Action, but merely an indication that GFRα1 and GFRα2 have been found to occur in some cells that do not express Ret. As the reason for this occurrence was unknown, the authors speculated that another Ret-like signaling molecule *may* be involved. Finally, the cited paragraph states that the authors "have analyzed neuroblastoma cell lines that express all three coreceptor proteins *and Ret*" (emphasis added). Again, the described cells are not DRG neurons that are Ret (-/-) and Ret-independent, as asserted in the Office Action.

It is thus apparent that the passages in Baloh cited in the Office Action have been misinterpreted. Applicants appreciate that Baloh teaches that the receptor for PSP is unknown, and that neither the Ret-GFRα1 nor Ret-GFRα2 receptor complexes form functional PSP receptors. However, Baloh does not conclude from this fact that a Ret-independent signaling pathway exists. Indeed, to the contrary, Baloh states that "an *additional* component is likely to be required for PSP signaling, either another PSP-specific coreceptor or an additional signaling component (3)." *See* Baloh, page 5801 (emphasis added). Similarly, Baloh's findings that GFRα3 was not capable of mediating Ret signaling for any known GFR ligands do no more than suggest the possible presence of additional receptor components that may effect signaling *through Ret*, or the existence of as yet undiscovered ligands that, when complexed with GFRα3 receptors, may activate *Ret-dependent intracellular signaling.*

Applicants further respectfully submit that although one of ordinary skill in the art may hypothesize, based on the findings reported by Baloh and others, either that additional

signaling components in addition to Ret may be present, or that an alternative Ret-like protein may exist to effect signaling of known GRF ligands through GFRα3, such an artisan would not interpret Baloh as suggesting that a Ret-independent pathways necessarily exists. At most, on the basis of the prior art, a skilled artisan would merely understand that everything about GFRα3, its naturally occurring ligands, and its intracellular signaling pathways was not known, and that further experimentation was needed. Such an invitation to experiment can hardly provide the requisite motivation to modify the prior art methods, or a reasonable expectation that such modification would succeed, as necessary to render the instant invention obvious under Section 103.

Applicants respectfully assert, therefore, that the assertions made with regard to the teachings of Baloh in the Office Action are based on a misinterpretation of the reference. Simply put, the teachings of Baloh, when properly construed, fail to overcome the deficiencies of the other references cited previously – references that the Examiner has already acknowledged fail to render the claimed invention obvious. As the foregoing clearly shows, the prior art, whether considered alone or in any proper combination, fails completely to establish the existence of the Ret-independent intracellular signaling pathway described in the instant application.

For these reasons and others, Applicants respectfully submit that the invention defined by the claims is not obvious in view of the cited art. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be reconsidered and withdrawn, and a Notice of Allowance for all of pending Claims 1 to 91 be issued.

In the event that the Examiner is not persuaded that the application is in condition for allowance, the Examiner is invited to telephone Applicants' undersigned representative to resolve any outstanding issues.

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